REMARKS

Claims 1, 2 and 4-24, 27 and 34-38 are currently pending in the present application. Claims 9-24 and 27 have been withdrawn from consideration. Claims 1, 2, and 4-8 have been amended herein, support for which may be found in the specification, at least, in Example 6. New claims 34-38 have been added, which correspond to present claims 4-8. Further, the specification has been amended as shown above, support for which may be found in the specification, at least, in Examples 2 – 10. No new matter has been added by way of the present amendments.

Objections to the Specification

The Examiner objected to the brief description of the drawings corresponding to Figures 1 – 12. In response, Applicants have amended the present specification to comply with the Examiner's request. Accordingly, Applicants respectfully request withdrawal of the outstanding objection.

Claim Objections

Claim 1 is objected to for employing incomplete sentence structure. Applicants have amended claim 1 in order to overcome the outstanding claim objection. Accordingly, withdrawal thereof is respectfully requested.

Rejection under 35 U.S.C. § 102(b)

Claims 1-5 and 8 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Ishikawa et al. (Exp. Hematol. 30(5):488-494; May 2002).[1]

[1] The Examiner cited "Ishikawa et al. Am. J. Transpl. 2:520-525, 2002" in the Office Action, however Applicants believe that this citation is incorrect and have replaced the citation as Applicants believe is correct.

Claim 1 has been amended in the present response to recite:

> 1. A newborn ***NOD/SCID/IL2rg-null*** mammal (excluding human), into which human-***derived hematopoietic stem or precursor cells*** have been transplanted, and which is able to generate immunocompetent cells derived from said human-derived hematopoietic stem or precursor cells and/or physiologically active substances derived from said immunocompetent cells. (emphasis added)

Additionally, claim 2 has been amended in a similar manner. Ishikawa does not teach a newborn NOD/SCID/IL2rg-null mammal as is presently recited in claims 1 and 2. Thus, Ishikawa cannot anticipate the presently claimed invention, within the meaning of 35 U.S.C. § 102(b). Reconsideration and withdrawal are respectfully requested.

Rejections under 35 U.S.C. § 103(a)

Claims 1, 6 and 7 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Ishikawa et al.("Ishikawa"), in view of Olive et al, (Immunol. Cell Biol. 76:520-525, 1998)("Olive").

The Examiner concludes that it would have been *prima facie* obvious for a person of ordinary skill in the art to combine the teachings of Ishikawa and Olive to introduce human hematopoietic cells into immature immunodeficient mice to produce human B cells and IgG with a reasonable expectation of success.

However, for the following reasons, Applicants respectfully submit that it would not have been obvious for a person of ordinary skill in the art to combine the teachings of Ishikawa and Olive and to arrive at the presently claimed invention.

First, the combination of Ishikawa and Olive does not teach or suggest the presently claimed invention. That is, Ishikawa and Olive does not teach a newborn NOD/SCID/IL2rg-null mammal into which human-derived hematopoietic stem or precursor cells have been transplanted ("the claimed mammal").

Second, the differences between the claimed invention and the combination of Ishikawa and Olive would not have been obvious to a person of ordinary skill in the art.

The claimed mammal has the following characteristics:

i) The claimed mammal is able to efficiently generate all components for a human hematopoietic system, including human erythrocytes, human megakaryocytes, or human thrombocytes (*See* Example 6, paragraphs 100 and 103 of the published application US 2006/0161996).

ii) The engraftment level of the human cells in each of the PB, the BM, and the spleen of the claimed mammal is significantly higher than that of the NOD/SCID/β2-microglobulin^{null} mice described in the Specification (*See* Example 6, paragraph 103 of the published application US 2006/0161996).

iii) The claimed mammal is able to generate cells at each stage of the development of B cells, namely, CD 19^{+}CD20^{hi} mature B cells (mature stage), CD10^{+}CD19^{+} immature B cells (immature stage), and CD34^{+}CD19^{+}pro-B cells (pro-B cells stage) (*See* Example 7, paragraph 105 of the published application US 2006/0161996).

iv) The claimed mammal is able to generate IgM^{+}B cells, IgD^{+}B cells, IgG^{+}B cells, and IgA^{+}B cells (*See* Example 7, paragraph 107 of the published application US 2006/0161996).

v) The claimed mammal is able to efficiently generate both human IgM and IgG Particularly, the generation level of human IgG in the claimed mammal is higher than that in the NOD/SCID/β2-microglobulin^{null} mice described in the Specification (*See* Example 7, paragraphs 109 and 110 of the published application US 2006/0161996).

vi) In the thymus gland of the claimed mammal, human CD4^{+}CD8^{+} T cells, human CD4^{+}CD8^{-} T cells, and human CD4^{-}CD8^{+}T cells form an organized structure. This means that human CB-stem cell-/precursor cell-derived T cells in the claimed mammal undergo maturation and growth stimuli (*See* Example 7, paragraph 114 of the published application US 2006/0161996).

vii) The claimed mammal is able to generate human-derived antigen-presenting cells, such as human dendritic cells and human monocytes which are necessary for the immune response to antigen (*See* Example 7, paragraphs 115 and 116 of the published application US 2006/0161996).

viii) The claimed mammal has a human mucosal immune system. For example, the intestinal villi of the claimed mammal contain both human $IgA^{+}B$ cells and human $CD3^{+}T$ cells (*See* Example 8, paragraph 119).

ix) The claimed mammal is able to generate antigen-specific human IgM and IgG (*See* Example 9, paragraph 123 of the published application US 2006/0161996).

x) The claimed mammal is able to generate alloantigen-specific human T cells (*See* Example 10, paragraph 130 of the published application US 2006/0161996).

In contrast, the mice described in Ishikawa and Olive do not have the above-described characteristics. As the Examiner acknowledged, Ishikawa does not teach detection of IgG in the NOD/SCID/β2-microglobulin deficient mice (*See* page 6 of Office Action). With regard to Olive, the humanized immune system reported by Olive is called "PBL-acid" in which long-term and stable human immune subsets and Ig cannot be supplied. The present humanized immune system is developed by the intravenous injection of self-renewing, long-term human hematopoietic stem cells. In addition, Olive does not teach that Hu-PBL-SCID mice may produce human immunoglobulin other than IgG, and it is not clear whether the mice can generate antigen-specific IgG. Moreover, the PBL-SCID mice described in Olive are 8-week-old mice. It should be noted that 8-week-old mice and newborn mice are totally different in BM/thymic microenvironment supporting human-stem-cells (HSCs) engraftment and T cell development. While newborn mice in the present invention can support all the characteristics of HSCs (i.e., self-renewal, multilineage differentiation, and long-term engraftment), PBL-SCID mice cannot. Additionally, it is well known in the art that the PBL-acid system has been designed to analyze short-term duration of human immunity.

Therefore, since the claimed mammal is significantly different from the mice described in Ishikawa and Olive, a person of ordinary skilled in the art would not have predicted the claimed invention based on the combined teachings of Ishikawa and Olive.

Third, the objective of the Ishikawa study is to provide a quantitative method for analysis of human hematopoietic stem cells by using NOD/SCID/β2-microglobulin^{null} mice (*See* page 488, "Objective" of Ishikawa). The objective of the Olive study is only to assess T cell engraftment in lymphoid tissue of Hu-PBL-SCID mice (*See* page 520, "Summary" of Olive). For achieving their objective, it is not necessary to replace NOD/SCID/β2-microglobulin^{null} mice or Hu-PBL-SCID mice with any other mice. Therefore, there is no reason that a skilled reader of Ishikawa and Olive would have been motivated to replace NOD/SCID/β2-microglobulin^{null} mice or Hu-PBL-SCID mice with the claimed invention in order to achieve their objective.

Therefore, for the reasons enumerated above, it would not have been obvious for a person of ordinary skill in the art to combine the teachings of Ishikawa and Olive to arrive at the claimed invention. Accordingly, Applicants respectfully submit that the outstanding rejection should be withdrawn.

In view of the foregoing, Applicants believe the pending application is in condition for allowance. A Notice of Allowance is earnestly solicited.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Monique T. Cole, Reg. No. 60,154 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.147; particularly, extension of time fees.

Dated: OCT 14 2008

Respectfully submitted,

MTC

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